REMARKS

As established in the Tables below, the issue of how much buffering agent (antacid) is to be combined with the proton pump inhibitor has ***always*** been before the Examiner, and the Examiner's arguments to the contrary fail on the clear record of this application. In the Advisory Action mailed April 19, 2002, the proposed amendments of March 25, 2002 were not entered because they were deemed by the Examiner to: (i) raise new issues that would require further consideration and/or search; (ii) raise the issue of new matter, and (iii) not place the application in better form for appeal by materially reducing or simplifying the issues for appeal. The Applicant traverses each of these assertions, and below sets forth the support for why the claims do not raise new issues or new matter.

As an initial matter, the Examiner is erroneous in stating that Applicant has inserted new matter in the specification by its most recent amendments to the same (filing of March 25, 2002). As shown in the "Version Marked to Show Changes" of the March 25, 2002 filing (hand-delivered to the Examiner before the interview), it is plain that such amendments to the specification relate solely to ***typographical errors*** and not to numeric amounts of buffering agents.

The present invention is directed to non-enteric coated pharmaceutical compositions containing an acid labile proton pump inhibitor (PPI) and a buffering agent, the latter of which acts to protect the PPI from acid degradation upon oral administration. Throughout the 27 months of prosecution and three interviews of this case, Applicant has repeatedly presented claims and arguments to support its position that the amount of buffer can be defined with functional language. In addition, Applicant has repeatedly presented claims and arguments ***specifically defining the amounts (in mg and mEq)*** of buffers in the composition. In response,

the Examiner has conducted searches of the prior art directed to PPI plus buffer (antacid) combinations, and made her various rejections and objections in the office actions of record herein. Applicant and the Examiner have discussed the cited references during the interviews.

Most recently, during the March 25, 2002 interview, Applicant walked the Examiner through the specification and pointed out specific support for each numerical range of buffering agent in the claims. Applicant then followed the Examiner's suggestions and narrowed the claims to include the specific numeric ranges of buffering agents.

In addition, to further assist the Examiner, the mEq of buffer per mg of PPI is calculated and presented below in Table Nos. 1-9 for Examples I-IV in the specification (pages 44-50). These Tables and calculations are express or inherent from the cited Examples from the Detailed Description of the specification as originally filed. As shown in these Tables, Applicant provides **specific examples for solid dosage forms containing buffer ranging from at least 0.3 mEq to at least 0.9 mEq per mg of PPI**. Further, Applicant provides a general range of 0.1 to 2.5 mEq buffer per mg of PPI applicable to liquid and solid dosage forms at pages 32-34 of the specification.

Table No. 1 Example IB: 10 mg PPI Tablet Formula

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Calcium lactate	175	308	+2	154	1.1
Calcium glycerophosphate	175	210	+2	105	1.7

Sodium bicarbonate	250	84	+1	84	3
Total mEq of Buffer					**5.8**
mEq buffer per mg PPI					**0.58**

Table No. 2 Example IC: 20 mg PPI Tablet Formula

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Calcium lactate	175	308	+2	154	1.1
Calcium glycerophosphate	175	210	+2	105	1.7
Sodium bicarbonate	250	84	+1	84	3
Total mEq of Buffer					**5.8**
mEq buffer per mg PPI					**0.29**

Table No. 3 Example ID: 20 mg PPI Tablet for Rapid Dissolution

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Calcium lactate	175	308	+2	154	1.1
Calcium hydroxide	50	74	+2	37	1.4
Calcium glycerophosphate	175	210	+2	105	1.7
Sodium bicarbonate	500	84	+1	84	6
Total mEq of Buffer					**10.2**
mEq buffer per mg PPI					**0.51**

Table No. 4 Example IE: 20 mg PPI Powder for Reconstitution for Oral Use

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Calcium lactate	175	308	+2	154	1.1
Calcium	50	74	+2	37	1.4

hydroxide					
Calcium glycerophosphate	175	210	+2	105	1.7
Sodium bicarbonate	500	84	+1	84	6
Total mEq of Buffer					**10.2**
mEq buffer per mg PPI					**0.51**

Table No. 5 Example IF: 10 mg PPI Tablet Formula

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Calcium lactate	175	308	+2	154	1.1
Calcium glycerophosphate	175	210	+2	105	1.7
Sodium bicarbonate	250	84	+1	84	3
Total mEq of Buffer					**5.8**

mEq buffer per mg PPI					**0.58**

Table No. 6 Example IG: 10 mg PPI Tablet Formula

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Calcium lactate	175	308	+2	154	1.1
Calcium glycerophosphate	175	210	+2	105	1.7
Sodium bicarbonate	400	84	+1	84	4.8
Total mEq of Buffer					**7.6**
mEq buffer per mg PPI					**0.76**

Table No. 7 Example II: 20 mg PPI Standard Tablet of PPI and Buffering Agent

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Sodium	975	84	+1	84	11.6

bicarbonate					
Total mEq of Buffer					**11.6**
mEq buffer per mg PPI					**0.58**

Table No. 8 Example III: 20 mg PPI Central Core Tablet

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Sodium bicarbonate	975	84	+1	84	11.6
Total mEq of Buffer					**11.6**
mEq buffer per mg PPI					**0.58**

Table No. 9 Example IV: 20 mg PPI Effervescent Tablets and Granules

Buffering Agent	**Weight (mg)**	**Molecular Weight**	**Valence Number**	**Acid Neutralizing Equivalent Weight**	**mEq of Buffer**
Potassium	312	100	+1	100	3.1

carbonate					
Sodium bicarbonate	958 - 1158	84	+1	84	11.4 - 13.8
Total mEq of Buffer					**14.5 - 16.9**
mEQ buffer per mg PPI					**0.73 - 0.85**

To assist the Examiner, support for Claims 23 and 622 is presented in Table Nos. 10 and 11, below.

Table No. 10 History and Support for Claim 23

Claim 23 (Originally presented by amendment June 25, 2001)	**Support in Specification or Claims**	**Citation**
A solid pharmaceutical composition in a dosage form that is not enteric-coated, comprising:	• "A solid oral pharmaceutical composition, comprising..." • "wherein said dosage form is not enteric coated or time-released." • Presented: Original filing Jan. 11, 2000	Claim 7, Jan. 11, 2000 Claim 7, Jan. 11, 2000
active ingredients consisting essentially of:	• "Compressed tablets are solid dosage forms prepared by compacting a formulation containing an active ingredient...."	Page 36, lines 28-30

	• Presented: By amendment on Dec. 20, 2001	
(a) a non-enteric coated proton pump inhibitor	• "Such dosage forms are advantageously devoid of any enteric coating or delayed or sustained-release delivery mechanisms,..." • Presented: By amendment on Dec. 20, 2001	Page 24, lines 19-21
selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole,	• "wherein said proton pump inhibitor is selected from the group consisting of omeprazole,... lansoprazole,... pantoprazole, rabeprazole,... perprazole [esomeprazole],... pariprazole, and leminoprazole." • Presented: Original filing Jan. 11, 2000	Claim 6, Jan. 11, 2000
or an enantiomer, isomer, derivative, free base, or salt thereof,	• "neutral form or a salt form, a single enantiomer or isomer or other derivative or an alkaline salt of an enantiomer of the same." • Presented: By amendment on Dec. 20, 2001	Page 26, lines 25-27
in an amount of approximately 5 mg to approximately 300 mg; and	• "The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range from approximately <2 mg/day to approximately 300 mg/day." • Presented: By amendment on Dec. 20, 2001	Page 28, lines 18-21:

(b) at least one buffering agent	• "at least one buffering agent...." • "Such dosage forms...comprise a PPI and at least one buffering agent to protect the PPI against acid degradation." • "Non-limiting examples of buffering agents which could be utilized in such tablets include sodium bicarbonate, alkali earth metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, aluminum hydroxide or aluminum magnesium hydroxide." • Presented: Original filing Jan. 11, 2000	Claim 6, Jan. 11, 2000 Page 24, lines 20-23 Page 37, lines 21-28
selected from the group consisting of sodium bicarbonate, potassium bicarbonate,	• "wherein the buffering agent is sodium bicarbonate...." • "Accordingly, examples of buffering agents include, but are not limited to, ...potassium bicarbonate,..." • Presented: Original filing Jan. 11, 2000	Claim 11, Jan. 11, 2000 Page 30, lines 29-31
a calcium salt, and	• "wherein the buffering agent comprises at least	Claim 51,

	one of calcium acetate, calcium glycerophosphate, calcium chloride, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, calcium gluconate, calcium glycinate, calcium maleate, and other calcium salts." • "Non-limiting examples of buffering agents which could be utilized in such tablets include... alkali earth metal salts such as calcium carbonate, calcium hydroxide, calcium lactate, calcium glycerophosphate, calcium acetate...." • Presented: By amendment on June 25, 2001	June 25, 2001 Page 37, lines 21-28
a magnesium salt	• "wherein the buffering agent comprises at least one of magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium carbonate, magnesium silicate, magnesium lactate, and other magnesium salts." • "Non-limiting examples of buffering agents which could be utilized in such tablets include...alkali earth metal salts such ...magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate...." • Presented: By amendment on June 25, 2001	Claim 50, Jun 25, 2001 Page 37, lines 21-28

in an amount of approximately 0.1 mEq to approximately 2.5 mEq per mg of proton pump inhibitor	• As shown in Table Nos. 1-9, the amount of buffering agent for the solid dosage form examples ranges from at least 0.3 to at least 0.9 mEq of buffer per mg of PPI. • "approximately 1 mEq . . . sodium bicarbonate per 2 mg omeprazole with a range of approximately 0.2 mEq . . . to 5 mEq . . . per 2 mg omeprazole." • **NB**: 0.2 mEq buffer per 2 mg PPI = 0.1 mEq buffer per mg of PPI 5 mEq buffer per 2 mg PPI = 2.5 mEq buffer per mg of PPI Thus: (i) 1 mEq buffer per 10 mg PPI = 0.1 mEq buffer per mg of PPI. (ii) 25 mEq buffer per 10 mg PPI = 2.5 mEq buffer per mg of PPI. • "The pharmaceutical composition is in a solid form prior to dissolution or suspension in an aqueous solution." • "The inventive composition can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, two-part tablet or capsule, effervescent powder, effervescent tablet,	Examples I - IV, pages 44-50. Page 32, lines 1-5 Page 33, lines 24-26 Page 24, lines 16-19

	capsule, effervescent powder, effervescent tablet, pellets and granules. " • "The inventive composition comprises dry formulations, solutions and/or suspensions of the proton pump inhibitors." • "the formulations of the present invention can also be manufactured in concentrated forms, such as tablets, suspension tablets and effervescent tablets or powders, such that upon reaction with water or other diluent, the aqueous form of the present invention is produced for oral, enteral or parenteral administration." • "the buffering agent is sodium bicarbonate in an amount of approximately 1 mEq to approximately 25 mEq." • Presented: By amendment on Dec. 20, 2001	Page 26, lines 28-30 Page 34, lines 16-22 Claim 11, Jan. 11, 2000
wherein the dosage form is selected from the group consisting of suspension tablet, chewable tablet, effervescent powder, and effervescent tablet.	• "dosage form selected from the group consisting of a powder, a tablet, a suspension tablet, a chewable tablet, a capsule, an effervescent powder, an effervescent tablet, pellets and granules, ..." • Presented: Original filing Jan. 11, 2000	Claim 7, Jan. 11, 2000

Table No. 11 History and Support for Claim 622

Claim 622 (Originally Presented Nov. 19, 2001)	Support in Original Specification or Claims	Citation
A method for treating an acid-caused	• "These conditions are caused by an imbalance between acid and pepsin production, called aggressive factors, and mucous, bicarbonate, and prostaglandin production, called defensive factors. • Presented: By amendment on March 25, 2002	Page 2, lines 4-7
gastrointestinal disorder in a subject in need thereof, comprising:	• "A method of treating gastric acid disorders comprising...." • "The inventive pharmaceutical composition...can be used for the treatment or prevention of gastrointestinal conditions including, ..." • Presented: Original filing Jan. 11, 2000	Claim 15, Jan. 11, 2000 Page 27, lines 19-28
administering to the subject a solid pharmaceutical composition in a dosage form that is not enteric-coated;	See Table No. 10, Above	
wherein the composition comprises active	See Table No. 10, Above	

ingredients consisting essentially of:		
(a) a therapeutically effective amount of a non-enteric coated proton pump inhibitor	See Table No. 10, Above	
selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole,	See Table No. 10, Above	
or an enantiomer, isomer, derivative, free base, or salt thereof	See Table No. 10, Above	
in an amount of approximately 5 mg to approximately 300 mg; and	See Table No. 10, Above	
(b) a buffering agent in an amount of approximately 1.0 mEq	• "The dosage range of omeprazole or other proton pump inhibitors such as substituted benzimidazoles and derivatives thereof can range	Page 28, lines 18-21

to approximately 150 mEq	from approximately <2 mg/day to approximately 300 mg/day." • "approximately 1 mEq . . . sodium bicarbonate per 2 mg omeprazole with a range of approximately 0.2 mEq . . . to 5 mEq . . . per 2 mg omeprazole." • **NB**: (i) 0.2 mEq buffer per 2 mg PPI = 0.1 mEq buffer per mg of PPI (ii) 2 mg/day PPI = 1 mEq/day (iii) 28 mg/day PPI = 700 mEq/day Thus: (i) 40 mg PPI = 100 mEq (ii) 30 mg PPI = 75 mEq (iii) 20 mg PPI = 50 mEq Thus: (i) 2 mg PPI = 1.0 mEq buffer (ii) 28 mg PPI = 70 mEq buffer • "The inventive composition can alternatively be formulated as a powder, tablet, suspension tablet, chewable tablet, capsule, two-part tablet or capsule, effervescent powder, effervescent tablet, pellets and granules. " • "The inventive composition comprises dry formulations, solutions and/or suspensions of the proton pump inhibitors."	Page 32, lines 1-5 Page 24, lines 16-19 Page 26, lines 28-30

	proton pump inhibitors." • "the formulations of the present invention can also be manufactured in concentrated forms, such as tablets, suspension tablets and effervescent tablets or powders, such that upon reaction with water or other diluent, the aqueous form of the present invention is produced for oral, enteral or parenteral administration." • "the buffering agent is sodium bicarbonate in an amount of approximately 1 mEq to approximately 25 mEq." • "The buffering agent is present in an amount of about 4 mEq to about 30 mEq." • Additionally, the specification states that the use of omeprazole in the examples is only illustrative and that other PPIs can be used in the composition in place of omeprazole. • Presented: By amendment on Mar 25, 2001	Page 34, lines 16-22 Claim 11, Jan. 11, 2000 Claim 46, Jun 25, 2001
selected from the group consisting of a bicarbonate salt of a group IA metal,	• "wherein the buffering agent comprises a bicarbonate salt of a Group IA metal." • "comprises a bicarbonate salt of Group IA metal as buffering agent...."	Claim 50, Jun 25, 2001 Page 31, lines 19-20

	• Presented: By amendment on June 25, 2001	
a calcium salt, and	See Table No. 10, Above	
a magnesium salt,	See Table No. 10, Above	
wherein the buffering agent is in an amount sufficient to elevate gastric acid pH of the subject's stomach	• "the buffering agent of the present invention, when in the presence of gastric acid, must only elevate the pH of the stomach sufficiently to achieve adequate bioavailability of the drug to effect therapeutic action." • Presented: By amendment on Dec. 20, 2001	Page 30, lines 24-28
to prevent or inhibit gastric acid degradation of the non-enteric coated proton pump inhibitor and achieve sufficient bioavailability of the proton pump inhibitor in the subject to elicit a therapeutic effect.	• "the buffering agent of the present invention, when in the presence of gastric acid, must only elevate the pH of the stomach sufficiently to achieve adequate bioavailability of the drug to effect therapeutic action." • "buffering agent...functions to substantially prevent or inhibit the acid degradation of the PPI by gastric acid sufficient to preserve the bioavailability of the PPI administered. The buffering agent is administered in an amount sufficient to substantially achieve the above functionality." • Presented: By amendment on Nov. 19, 2001	Page 30, lines 24-28 Page 30, lines 15-24

The Examiner has also contended that the functional language of Claim 622 regarding the amount of buffer could not be determined by one skilled in the art because no specific numeric range of the buffer amount was provided. Applicant argued, among other things, that the use of a functional limitation is permissible, and indeed reviewed the pertinent sections of the MPEP (MPEP § 2173.05 (g)) with the Examiner confirming the same. The Examiner nevertheless continued to be ambivalent about the use of such functional language contending that the skilled artisan would not know how to make such a tablet or capsule and put it "on the shelf" unless the skilled person was provided with a specific amount. Accordingly, despite the fact that:

(i) the patent law permits such functional language,

(ii) the specification provides clear guidance to determine an amount of buffering agent to formulate a composition and "put it on the shelf," and

(iii) the prior art fails to preclude such functional language,

Applicant has amended its claims by adding a ***numeric range of buffering agents*** to independent Claim 622 Applicant again reserves its right to pursue any amended or cancelled subject matter in this or a related case. None of such subject matter is disclaimed or otherwise dedicated to the public.

Finally, as Applicant emphasized to the Examiner during the March 25, 2002 interview, the Examiner's notation of "cursory reviewed" on Applicant's Information Disclosure Statements in this (and its related cases) is improper under PTO rules. During the interview, Applicant requested the supporting legal citation for such action, but the Examiner provided none. In the Interview Summary, the Examiner stated that "References of record used for rejections and references discussed in the interviews have been carefully considered by the examiner." These references include at least:

(1) U.S. 4,786,505, by Lovgen, *et al.;*

(2) U.S. 5,44,918, by McCullough;

(3) U.S. 5,840,737, by Phillips;

(4) U.S. 5,792,473, by Gergely, *et al.*;

(5) Japanese Patent Appln. No. 05255088;

(6) Japanese Patent Appln. No. 055194225, by Oishi, *et al.*

(7) Japanese Patent Appln. No. 055194224, by Oishi, *et al.*

(8) Japanese Patent Appln. No. 05294831;

(9) EP 670160, by Gergely, *et al.;*

(10) Quercia, *et al.*, Abstract of ASHP Midyear Clinical Meeting, Vol. 31, p. P-51E (Dec. 1996);

(11) Carroll and Trudeau Abstact from 10th World Congress of Gastroenterology (Oct. 1994);

(12) Phillips, Critical Care Med. Suppl. (Jan. 6, 1995);

(13) Pilbrant, et al., "Development of An Oral Formulation of Omeprazole," Scand. J. Gastrolenterol, Vol. 20, (Suppl. 108) pp. 113-120 (1985);

(14) Pilbrant, "Principles for Development of Antacids," Scand. J. Gastroenterol Suppl., Vol. 75, pp. 32-36 (1982);

(15) Andersson, T., "Pharmacokinetics and Bioavailability of Omeprazole After Single and Repeated Oral Administration in Healthy Subjects," et al., Br. J. Clin. Pharmac., Vol. 29, pp. 557-563 (1990);

(16) Andersson, T., et al., "Pharmacokinetics of Various Single Intravenous and Oral Doses of Omeprazole," European Journal of Clinical Pharmacology, Vol. 39, pp. 195-197 (1990);

(17) Landahl, S., et al.,"Pharmacokinetic Study of Omeprazole in Elderly Healthy Volunteers" by Clin. Pharmacokinet., Vol. 23, No. 6, pp. 469-476 (1992).

Applicant again respectfully requests that the Examiner's "cursory reviewed" statements be withdrawn and that the Examiner confirm that she has fulfilled her duty under the rules in considering all references of record (*See* MPEP § 609(C)(2)). Applicant also hereby reserves its right to petition the Commissioner on this issue.

CONCLUSION

It is respectfully submitted in view of the foregoing Remarks that the proposed amendments of both Applicant's March 25, 2002 Amendments and Responses should be admitted and considered by the Examiner in this case. Therefore, with entry of these amendments, it is submitted that all of the objections and rejections in the Office Action dated February 1, 2001 have been overcome and should be withdrawn. Applicant respectfully requests early and favorable notification to that effect. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

THE CURATORS OF THE
UNIVERSITY OF MISSOURI

By: MAYER, BROWN, ROWE & MAW,

By: _____
Joseph A. Mahoney (Reg. No. 38,956)

Dated: May 1, 2002

MAYER, BROWN, ROWE & MAW
P.O. Box 2828
Chicago, IL 60609-2828
(312) 701-8979